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Impact of pregnancies on ovarian cancer

Risk, prognosis and tumor biology

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Abstract

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Ovarian cancer is the most lethal gynecological malignancy. The etiology is complex and not fully understood, partly since ovarian cancer is not one distinct disease, but rather several histologically and clinically different subtypes. The two main groups are epithelial (90%) and non-epithelial (10%) cancers, further divided into five epithelial and two main non-epithelial subtypes. Women who have given birth have a lower risk of developing epithelial ovarian cancer, and the risk is further reduced with each additional childbirth. However, the association between several pregnancy-related factors, such as pregnancy length, maternal age at birth, offspring size, and subsequent risk of ovarian cancer has been unclear. In addition, the impact of pregnancy-related risk factors on non-epithelial ovarian cancer is unknown. Further, the underlying mechanism behind the protection of childbirth has not been revealed and the prognostic impact of pregnancies is not established.

In my first two studies, I evaluated associations between pregnancy-related factors and risk of epithelial ovarian cancer and its different subtypes [Study I] and non-epithelial ovarian cancer [Study II]. These case-control studies were based on linked data from the population-based medical birth registers and cancer registers in Denmark, Finland, Norway and Sweden. In Study I, preterm birth was associated with an increased risk of epithelial ovarian cancer among parous women, whereas increased number of births and pregnancies at older age were associated with decreased risk. In Study II, increasing age at last birth was associated with lower risk of sex cord-stroma cell tumors (SCSTs), as was shorter time since last birth.

In Study III, the prognostic impact of parity on both epithelial and non-epithelial ovarian cancer by subtype was investigated by linkage of data from the Swedish medical birth register, the cancer register and the cause of death register. Parity was associated with reduced cancer-specific mortality in ovarian germ cell tumors. We found no prognostic impact of parity in patients with SCSTs or epithelial ovarian cancer.

In Study IV, we investigated whether hormones and proteins involved in pregnancy and tumor development differed according to the woman's parity status in patients with high-grade serous ovarian cancer. Parous women more often had progesterone receptor (PR) positive tumors, in comparison with nulliparous women, and increased number of children was associated with PR positive tumors.

In summary, a woman's reproductive history will not only impact on the risk of developing ovarian cancer, but also have a long-lasting influence on the tumor biology.

Keywords: Epithelial ovarian cancer, non-epithelial ovarian cancer, reproductive history, parity, risk factor, survival, progesterone receptor

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Fortsätt när mörkret kommer och allt gör ont
Fortsätt som ett höstlöv i vårens första flod
Som ett hjärta som vägrar sluta slå
När varje bön gått åt, fortsätt

För jag tror
När vi går genom tiden
Att allt det bästa
Inte hänt än

Håkan Hellström: ”Du är snart där”

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. Sköld C, Bjørge T, Ekbom A, Engeland A, Gissler M, Grotmol T, Madanat L, Gulbech Ording A, Stephansson O, Trabert B, Tretli S, Troisi R, Toft Sørensen H, Glimelius I. **Preterm delivery is associated with an increased risk of epithelial ovarian cancer among parous women.** *International Journal of Cancer* 2018 Oct 15;143(8):1858-1867.

II. Sköld C, Bjørge T, Ekbom A, Engeland A, Gissler M, Grotmol T, Madanat L, Gulbech Ording A, Trabert B, Tretli S, Troisi R, Toft Sørensen H, Glimelius I. **Pregnancy-related risk factors for sex cord-stromal tumours and germ cell tumours in parous women: A registry-based study.** *British Journal of Cancer* 2020 Jul;123(1):161-166.

III. Sköld C, Koliadi A, Enblad G, Stålberg K, Glimelius I. **Parity is associated with better prognosis in ovarian germ cell tumors, but not in other ovarian cancer subtypes.** *Submitted.*

IV. Sköld C, Tolf A, Corvigno S, Dahlstrand H, Stålberg K, Enblad G, Sundström Poromaa I, Mezheyeuski A, Glimelius I, Koliadi A. **Association between parity, histopathological tumor features and survival in high-grade serous ovarian cancer.** *Manuscript.*

Contents

Abbreviations

AFP	Alpha-fetoprotein
BEP	A chemotherapy combination of bleomycin (B), etoposide (E) and cisplatin (P)
BRAF	Proto-oncogene encoding the serine/threonine-protein kinase B-RAF (Rapidly Accelerated Fibrosarcoma)
BRCA1	Breast Cancer 1 gene; tumor suppressor gene
BRCA2	Breast Cancer 2 gene; tumor suppressor gene
CA 125	Cancer Antigen 125; tumor biomarker for ovarian cancer
CDK	Cyclin-dependent kinase
CI	Confidence Interval
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
FIGO	International Federation of Gynecology and Obstetrics
GCT	Germ cell tumor
HCG	Human Chorionic Gonadotropin
HIPEC	Hyperthermic Intraoperative Intraperitoneal Chemotherapy
HGSOC	High-grade serous ovarian cancer
HR	Hazard Ratio
ICD	International Statistical Classification of Disease
KRAS	Proto-oncogene identified in Kirsten rat sarcoma virus, encoding the GTPase protein KRAS
LDH	Lactate dehydrogenase
MBR	Medical birth register
NSAID	Non-steroid anti-inflammatory drug
OS	Overall survival
PARP	Poly (ADP-ribose) polymerase
PCOS	Polycystic ovarian syndrome
PFS	Progression free survival
PGRMC1	Progesterone receptor membrane component 1
PR	Progesterone receptor
SCST	Sex cord-stromal tumor
STIC	Serous tubal intraepithelial carcinoma

TMA	Tissue microarray
TGFβ1	Transforming growth factor beta 1
TP53	Tumor Protein 53; tumor suppressor gene
VEGF-A	Vascular Endothelial Growth Factor A

Introduction

The impact of pregnancy and pregnancy complications on future health and disease of women is of great interest today. More specifically, this is of importance in diseases that affect the reproductive organs, such as ovarian cancer. Women tend to live longer, have fewer pregnancies and are older when they begin their childbearing than earlier generations. This will cause a change in the anticipated panorama of malignancies affected by pregnancies, as well as an increased risk of pregnancy and cancer diagnosis coinciding.

It is well established that women who have given birth have a lower risk of developing epithelial ovarian cancer, and the risk is further reduced with each additional childbirth. However, the impact of several pregnancy-related factors, such as preeclampsia, pregnancy length, maternal age at birth and offspring size, and subsequent risk of ovarian cancer has been unclear. In addition, the impact on the different subtypes of epithelial ovarian cancer has not been established. Further, whether or not these factors influence the risk of non-epithelial ovarian cancer has not been known. Nor has the underlying mechanism behind the protection of childbirth on epithelial ovarian cancer been revealed. These issues are all addressed in my thesis.

Ovarian cancer has no easily detectable premalignant phase, making early diagnosis difficult. Few risk factors are preventable, hence there is a need to identify protective factors. Moreover, long term survival has only increased marginally, highlighting the need of preventive work and better therapies. My goals are to increase our knowledge of the impact of pregnancies on ovarian cancer and hopefully help us develop new strategies in both preventing and treating this highly lethal disease.

Background

Ovarian cancer

Ovarian cancer is the most lethal gynecological malignancy, mainly due to diagnosis at late stage. Early symptoms are often unspecific, like urinary frequency and constipation, and when more pronounced symptoms occur, the cancer has most often already spread outside the ovaries with poor chances of cure. The incidence in the Nordic countries is among the highest in the world with 9.2 cases per 100,000 women-years. In Sweden, around 700 women are diagnosed each year and it is the fifth most common cause of cancer-related death among women (1). The etiology of ovarian cancer is complex and not fully understood, partly because ovarian cancer is not one distinct disease, but rather several histologically and clinically different subtypes, with two main groups, epithelial (90%) and non-epithelial (10%) cancers. Cancers originating in the fallopian tube and peritoneum are included as an entity of epithelial ovarian cancer concerning pathogenesis, prognosis and treatment.

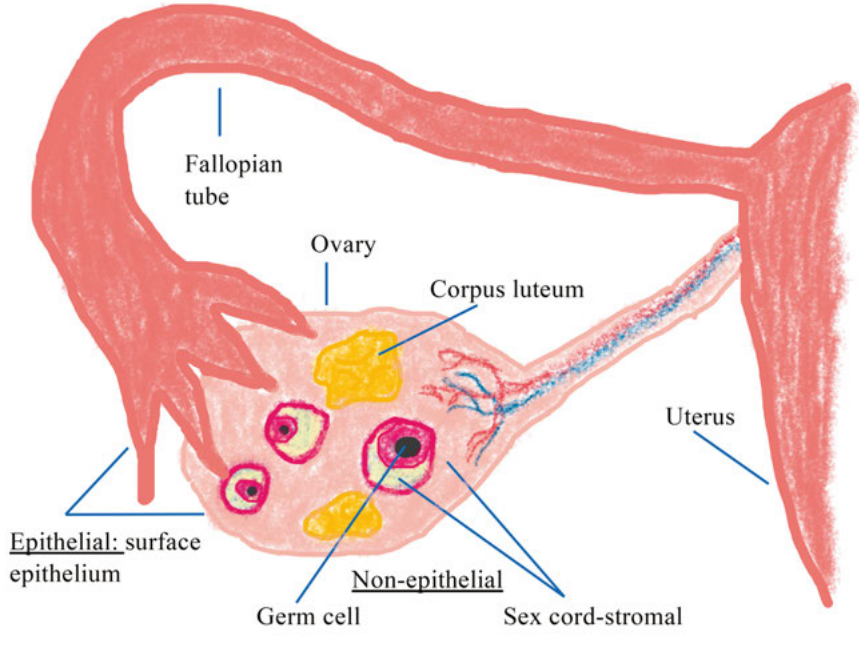

Figure 1. Cell of origin for the different ovarian cancer subtypes.

Staging

Both epithelial and non-epithelial ovarian cancer are staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system (2).

Table 1. FIGO staging for cancer of the ovary, fallopian tube and peritoneum.

Stage I	Tumor confined to the ovaries/fallopian tubes
Stage II	Tumor involves ovaries/fallopian tubes with extension in pelvis; or peritoneal cancer
Stage III	Tumor involves ovaries/fallopian tubes/ peritoneum, with cytologically/ histologically confirmed spread to peritoneum outside the pelvis/ metastasis to retroperitoneal lymph nodes
Stage IV	Distant metastasis excluding peritoneal metastases

The ovaries and fallopian tubes are situated in the pelvis, in close proximity to other organs and without physical barriers. This makes it possible for the cancer to spread by direct extension and exfoliation of cancer cells into the ascitic fluid in the peritoneal cavity, and then implant predominately to the peritoneum. Lymphatic spreading to pelvic and para-aortic lymph nodes is also common, while hematogenous dissemination is rare (3). Standard treatment includes extensive surgery and postoperative platinum-based chemotherapy, with the addition of targeted therapies for specific patient groups, described in more detail later.

Epithelial ovarian cancer

Epithelial ovarian cancer is subdivided in histologically, genetically and clinically distinct subtypes: high grade serous (70%), clear cell (10%), endometrioid (10%) mucinous (5%), and low-grade serous (5%) adenocarcinoma. The histology of fallopian tube and primary peritoneal cancer is predominantly high grade serous.

Table 2. Description of epithelial ovarian cancer subtypes

High-grade serous carcinoma 70%	Fast growing, 95% diagnosed at advanced stage Genetically unstable >95% with *TP53*-mutations Associated with *BRCA1/BRCA2*-mutations Cell of origin: distal fallopian tube
Endometrioid carcinoma 10%	~50% diagnosed at stage I Associated with endometriosis 10-20% synchronic endometrial cancer Often estrogen and progesterone-receptor positive Cell of origin: cystadenomas/endometriosis
Clear cell carcinoma 10%	~50% diagnosed at stage I Associated with endometriosis and Lynch syndrome Relatively chemo-resistant Associated with risk of thrombo-embolic events and paraneoplastic hypercalcemia Cell of origin: cystadenomas/endometriosis
Mucinous carcinoma 5%	Often large tumors diagnosed at early stage Relatively chemo-resistant Historically often mis-classified gastrointestinal tumors ~50% with *KRAS/TP53*-mutations Cell of origin: mucinous borderline tumors
Low-grade serous carcinoma 5%	Often diagnosed at more advanced stage Indolent growth Relatively chemo-resistant 70% with specific mutations, e.g., *KRAS/BRAF* Cell of origin: serous borderline tumors

The carcinogenesis of epithelial ovarian cancer has been described by a dualistic model, with two pathways involving different precursor lesions (4). Mucinous, clear cell, endometrioid, and low-grade serous tumors are thought to develop from transformation of implant cysts on the ovary and have a better prognosis, while high-grade serous ovarian cancer (HGSOC) is thought to

develop predominantly from premalignant lesions in the fallopian tube (serous tubal intraepithelial carcinoma, STIC) and have a poorer prognosis (5). The assumption of tubal origin of HGSOC is based on findings that HGSOC histologically as well as molecularly resemble cells of the distal fallopian tubes, and STIC is often found in patients with HGSOC (6-8). Further, STIC is often noted in *BRCA*-mutation carriers after prophylactic salpingo-oophorectomy (9, 10). Surgical removal of the fallopian tubes reduces the risk of epithelial ovarian cancer (11), and the performance of opportunistic salpingectomy in postmenopausal women undergoing benign pelvic surgery is recommended (12).

Median age at diagnosis is 63 years. The five-year overall survival (OS) is below 50% (13), mainly due to the fact that the vast majority of cases are diagnosed with FIGO stage III and IV disease. Patients diagnosed with FIGO stage I have an excellent prognosis (89% five-year cause-specific survival (14)), emphasizing the importance of early diagnosis. Unfortunately, screening trials have not been successful (15). The most frequently used tumor marker in clinic is cancer antigen 125 (CA 125), with elevated serum levels in 80% of all patients with non-mucinous epithelial ovarian cancer. The biomarker is used both at diagnosis, in monitoring response to treatment, and in detection of recurrent disease (16).

Primary treatment

Surgery

Primary treatment of ovarian cancer is surgery, aiming at removing all visible cancer from the abdomen. Surgery includes extirpation of uterus, bilateral salpingo-oophorectomy and omental resection, and removal of all visible and palpable cancer. In stage I, lymphadenectomy is performed for staging. Advanced stage surgery often includes bowel resections, splenectomy, and diaphragmatic and liver resection (16). Two randomized trials have compared neoadjuvant chemotherapy followed by interval surgery with primary debulking surgery with similar results (17, 18). However, both studies have been questioned, especially due to low rate of complete cytoreduction and low survival rate. Today, neoadjuvant treatment is only indicated in patients with extensive disease with risk of not achieving optimal primary cytoreductive surgery, and for patients whose general condition makes it difficult to withstand aggressive initial surgery. An ongoing randomized trial will hopefully provide more evidence on whether neoadjuvant chemotherapy should be considered for more patient groups (19).

Chemotherapy

Postoperative chemotherapy is indicated for all patients with epithelial ovarian cancer, except for those with stage IA-B of certain histologic subtypes. The

golden standard for postoperative treatment is the combinations of carboplatin and paclitaxel administered intravenously every third week for six cycles (16). Most common adverse effects are hematological toxicity, fatigue, nausea, muscle pain, peripheral neuropathy, and alopecia.

Since the 1990s, the gyne-oncology community has continuously strived to improve the efficacy of adjuvant treatment. Over time, several randomized trials have evaluated the effect of different chemotherapy regimens, including adding a third agent (20-26); giving sequential treatment (26, 27); high-dose therapy (28) and dose-dense therapy (chemotherapy given more frequently) (29-33). To date, no study proved to be better than the standard treatment with carboplatin/paclitaxel.

Intraperitoneal chemotherapy treatment

The intraperitoneal spreading of ovarian cancer makes it relevant to evaluate intraperitoneal administration of chemotherapy, since local high-dose-intensity can be achieved without higher intravenous concentration. A Cochrane analysis showed improved PFS and OS in women with stage III ovarian cancer after optimal debulking surgery, but catheter-related complications were common and toxicity increased (34). A more recent study, where bevacizumab was added to the treatment, could not confirm better survival among patients receiving intraperitoneal compared to intravenous chemotherapy (35). In Sweden, intraperitoneal chemotherapy, as well as hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC), is not recommended outside clinical trials.

PARP-inhibitors

In Sweden, poly (ADP-ribose) polymerase (PARP) inhibitors are indicated as maintenance treatment in patients with stage III-IV disease with a *BRCA1* or *BRCA2*-mutation, with complete or partial response after postoperative chemotherapy. The European Medicines Agency (EMA) has granted use of PARP-inhibitors in primary treatment of advanced ovarian cancer regardless of *BRCA*-mutation status. PARP-inhibitors are generally well-tolerated, but nausea, anemia, thrombocytopenia and fatigue are relatively common side-effects.

Single-strand breaks in the DNA occur frequently in all proliferating cells. PARP are important enzymes involved in repairing these single- strand breaks, that will otherwise subsequentially cause double-strand breaks of the DNA. By inhibiting PARP, the repair of single strand breaks is prevented. Cells with a proficient homologous repair system will repair the double strand breaks and ensure genomic stability. Cells with mutations in the *BRCA1* or *BRCA2* genes have a deficient homologous repair system. These cells can therefore not repair the accumulating double-strand breaks, which will result in apoptosis (36). In patients with a *BRCA1* or *BRCA2*-mutation, treatment with PARP-inhibitors resulted in a remarkable increase in PFS, also with

effect in patients with homologous repair deficiency without *BRCA*-mutations (37-40).

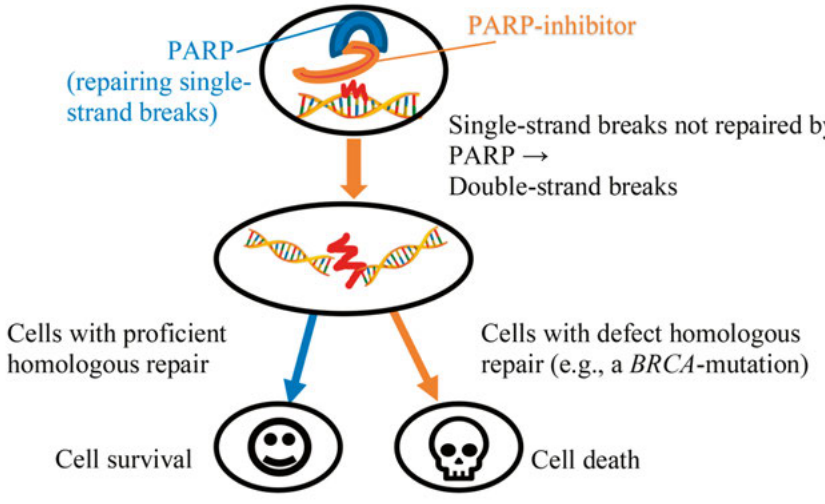

Figure 2. Mechanism of action of PARP-inhibitors

Bevacizumab

Patients who lack a BRCA mutation and are at high risk of relapse have a limited beneficial effect from adding the monoclonal antibody bevacizumab to the chemotherapy. This group includes patients with advanced disease who underwent debulking surgery but had macroscopic residual disease and FIGO stage III or IV. Bevacizumab is also recommended to inoperable patients (16).

Bevacizumab inhibits the vascular endothelial growth factor A (VEGF-A) and is administered intravenously every three weeks in combination with the postoperative chemotherapy, and continued as maintenance therapy for an additional 15 cycles. Side-effects include hypertension, proteinuria/nephrotic syndrome, thrombo-embolic events, bowel perforation, fistulations and bleedings.

Treatment of recurrent disease

Despite optimal primary treatment, up to 80% of epithelial ovarian cancer patients will relapse within a few years. The choice of treatment of recurrent disease is based on the platinum-free interval. Tumors are classified as platinum-sensitive if the interval from last course of platinum-treatment is longer than six months; and as platinum-resistant if time to relapse is shorter than six months, or when progressing during treatment.

Patients with platinum-sensitive disease are likely to respond to repeated treatment with platinum-based chemotherapy combinations (carboplatin in combination with pegylated liposomal doxorubicin, paclitaxel or

gemcitabine), and selected patients will benefit from repetitive surgery. Treatment with PARP-inhibitors can prolong PFS in patients responding to chemotherapy treatment (41).

Platinum-resistant ovarian cancer is associated with worse prognosis. In this setting, chemotherapy is predominantly given as monotherapy, with paclitaxel, gemcitabine, pegylated liposomal doxorubicin and topotecan as the most effective drugs, with some additive effect by bevacizumab. The dismal prognosis for patients with platinum-resistant disease highlights the need of further research to develop better treatment strategies (42).

Non-epithelial ovarian cancer

Non-epithelial ovarian tumors represent a heterogeneous group of malignancies originating from the interior of the ovaries (Figure 1). The two main subgroups are germ cell tumors (GCTs) and sex cord-stromal tumors (SCSTs), each with several subtypes.

Table 3. Subtypes of non-epithelial ovarian cancer

Germ cell tumors	**Sex cord-stromal tumors**
Dysgerminoma (~30%)	Granulosa cell tumors (~90%)
Yolk sack tumor (15-20%)	-juvenile (5%) and adult (95%) type
Teratoma (~35%)	Sertoli-Leydig cell tumors
Non-gestational choriocarcinoma	Theca cell tumors
Embryonal carcinoma	
Carcinoid	**Others**
Stroma ovarii, malignant	Small cell carcinoma
Polyembryoma	Sarcoma

Germ cell tumors

GCTs are rare in adults but account for 70% of the ovarian malignancies diagnosed in women younger than 30 years (43, 44). GCTs develop from the egg-producing germ cells of the ovary and are similar to GCTs in the testis; dysgerminoma is the female form of testicular seminoma (45). The incidence of both ovarian and testicular GCTs differs by geographic region. Ovarian GCTs have the highest incidence in Eastern Asia (46), while testicular GCTs are more common in Europe (47). Although GCTs are highly malignant, rapidly growing tumors, women with GCTs are most often diagnosed with stage I disease. Prognosis is excellent; five-year cause-specific survival exceeds 90% (14). Many GCT subtypes produce hormones that can be used as tumor markers: human chorionic gonadotropin (hCG) in choriocarcinomas, embryonal carcinomas and some dysgerminomas; alpha-fetoprotein (AFP) in yolk

sack tumors, embryonal carcinomas, mixed germ cell tumors and some teratomas. In dysgerminomas, lactate dehydrogenase (LDH) can be used as a tumor marker.

Sex cord-stromal tumors

SCSTs occur in women of all ages, with median age at diagnosis of 50 years, and many of the tumors produce hormones (48). The different subtypes of SCSTs develop from either the sex cord (granulosa cell tumors and Sertoli cell tumors), the stromal cells (theca cell tumors and Leydig cell tumors), or both (Sertoli-Leydig cell tumors). Granulosa cell tumors is the most common subtype, often presenting with large tumors producing estrogen. The high estrogen levels can cause endometrial hyperplasia, and endometrial cancer is seen in 5-10% of patients (49). In patients diagnosed with Sertoli-Leydig cell tumors, virilization due to androgen production is more common than estrogenic effects. Inhibin, AMH and CA 125 are used as tumor markers. The prognosis is generally good with nearly 90% relative survival at five years, mainly since the majority of SCSTs are diagnosed in stage I (14, 50).

Primary treatment

The different subtypes of GCTs and SCSTs are managed individually. General principles for primary treatment are described below. As in epithelial ovarian cancer, surgery is a cornerstone of the primary treatment of non-epithelial ovarian cancer. Even advanced stages can often be operated with fertility-sparing techniques (51, 52).

Germ cell tumors

Most subtypes of GCTs are fast growing and highly sensitive to chemotherapy, and prompt start of postoperative chemotherapy is indicated at all stages with the exception of stage IA-B with certain histological features. In analogy with treatment of GCTs in men, the most common chemotherapy regimen is BEP, a combination of bleomycin (B), etoposide (E) and cisplatin (P) for 3-4 cycles (51, 52). Side effects include hematological toxicity, nausea, fatigue, alopecia, pneumonitis, renal impairment and hearing impairment.

Sex cord-stromal tumors

Postoperative chemotherapy is recommended for patients with stage II-IV. The most commonly used regimen is three cycles of BEP, but six cycles of carboplatin and paclitaxel can be considered (as in epithelial ovarian cancer) (48, 51, 52).

Treatment of recurrent disease

Relapses of GCTs are rare, and the majority occurs within two years (52). Patients with SCSTs have a risk of relapse even several decades after diagnosis (53). Choice of treatment depends on subtype, and include repetitive surgery, chemotherapy, hormone treatment and radiotherapy (51).

Epidemiology

Epithelial ovarian cancer

A family history of breast- or ovarian cancer is well established as a risk factor of epithelial ovarian cancer. Approximately 20-25% of all ovarian cancer cases are associated with hereditary factors, with *BRCA1/BRCA2* and Lynch syndrome being the most common underlying mutations.(54) *BRCA1* and *BRCA2* are autosomal dominant inherited tumor suppressor genes, with a vital function in repairing double-strand DNA-breaks through homologous recombination. Prospective studies have found women with mutated *BRCA1* or *BRCA2*-genes to have a risk of developing ovarian cancer before the age of 80 of 40-60% and 10-25% (55-57), respectively. The risk of ovarian cancer increases from 40 years for *BRCA*1-mutation and 50 years for women with a *BRCA2*-mutation (58).

Environmental factors that increase risk include obesity and being tall (59), having endometriosis (clear cell and endometrioid subtype) (60), use of hormonal replacement treatment (61) and smoking (mucinous subtype) (62). Tubal salpingectomy and ligation reduce risk (11, 63), as well as oral contraceptive use (64). The protective effect of oral contraceptive use has been estimated to 20-30% after 5 years of use (65), however, a more recent study indicates that more contemporary formulations of oral contraceptives provide less prominent, if any, protection (66). Intrauterine devices have not been as well studied as oral contraceptives, but long-term use seems to provide a protective effect (67). Being older at menarche or younger at menopause (64, 68), hence, a shorter ovulatory period, seem to provide a weak protective effect against epithelial ovarian cancer. Nulliparity has been a known risk factor for ovarian cancer since the 1970s (69), and since pregnancy-related factors are of particular interest in ovarian cancer, they are further discussed below and are a main focus of the thesis. Many of the above-mentioned factors do not affect all subtypes of ovarian cancer, or affect the subtypes differently, which is also further addressed.

Non-epithelial ovarian cancer

Little is known about the etiology and molecular origins of GCTs and SCSTs or their risk factors, likely due to the heterogeneity of this group of neoplasms and their low incidence (51, 52). Gonadal dysgenesis, secondary to

chromosomal disorders, increases the risk of GCTs (70). The incident of GCTs differs with geographic region, with highest incidence rates in women in East Asia (46), suggesting that genetic or environmental risk factors might be of importance. Due to the penetrance of the disease in young women especially, factors related to puberty, childbearing and hormone changes during young adulthood are areas of particular interest. The lack of knowledge in this field identifies an unmet need and led me to focus part of this thesis work on childbearing and the risk and prognosis of non-epithelial ovarian cancer.

Pregnancy-related risk factors

Epithelial ovarian cancer

The risk of epithelial ovarian cancer is lower in parous women, with additional protection provided by each childbirth. Parity provides protection against all subtypes, although of different magnitude. The protective effect seems to be most pronounced in clear cell and endometrioid ovarian cancer (50-70% risk reduction), and less striking in the mucinous and serous subtypes (20-40%) (64, 71-75). In addition to the pregnancy itself, breastfeeding seems to provide additional protection, although results are somewhat conflicting (64, 76). Incomplete pregnancies are not protective for ovarian cancer; hence, the protective effect seems to be provided by longer duration of pregnancy (77). However, studies on pre-and post-term pregnancies have shown conflicting results (78, 79). Results have also been conflicting for other pregnancy-related factors such as maternal age at first and last birth (71, 73, 80-84), birth weight (79, 81), preeclampsia (81, 85) and multiple pregnancies (81, 86, 87). Infertility and infertility treatment have not been convincingly associated with ovarian cancer risk (88), although these factors are complex and difficult to study.

Non-epithelial ovarian cancer

The impact of number of births and age at birth on risk of GCTs or SCSTs remains unclear. Studies evaluating reproductive factors have been small (typically including less than 80 cases) (89-92). The largest study published to date, including 149 GCTs and 330 SCSTs, reported decreasing risk of GCTs and SCSTs with increased number of births (80). Intrauterine factors have been suggested to have an impact on the risk of both GCTs and SCSTs in the mother (90, 93) as well as in the offspring (94, 95). Results from previous studies on associations between parity, number of births and age at birth and risk of GCTs and SCSTs are summarized in Table 4.

Table 4. Risk of SCSTs and GCTs by parity, number of births, and age at birth.

Study (year)	Cases (n)	Variables adjusted for	Study period	Results
Boyce et al. (2009) (91)	SCSTs: 72	Race and age	1988-2008	Nulliparity: SCSTs: increased risk. Number of births: SCSTs: No ass. Age at births: Not investigated. Age at childbirth not investigated.
Sanchez-Zamorano et al. (2003) (92)	SCSTs: 10; GCTs: 18	Hormonal contraceptives and parity	1995-1997	Nulliparity: SCSTs: increased risk. GCTs: no ass. Number of births: SCSTs: decreased risk. GCTs: no ass. Age at births: SCSTs: decreased risk with high-age childbirths. GCTs: no ass. **High-age at childbirth protects against SCSTs ↓**
Abrektsen et al. (1997) (90)	SCSTs: 41; GCTs: 71	Number of births	1960-1991	Nulliparity: SCSTs: no ass. GCTs: no ass. Number of births: SCSTs: no ass. GCTs: no ass. Age at births: SCSTs: no ass. GCTs: increased risk with high-age childbirths. **Age at childbirth not associated with SCSTs ↔**
Adami et al. (1994) (80)	SCSTs: 330; GCTs: 149	Number of births, age at first birth	1958-1984	Nulliparity: Not investigated. Number of births: SCSTs: decreased risk. GCTs: no ass. Age at births: SCSTs: trend to decreased risk with high-age childbirths. GCTs: no ass. **Age at childbirth potentially associated with SCSTs ↓?**
Horn-Ross et al. (1992) (89)	SCSTs: 45; GCTs: 38	Age, study, year of birth, oral contraceptives, parity	1975-1982	Nulliparity: SCSTs: no ass. GCTs: no ass. Number of births: SCSTs: no ass. GCTs: no ass. Age at births: SCSTs: increased risk with high age. GCTs: not evaluated. **High-age at childbirth increases risk of SCSTs ↑**

Prognostic and predictive factors

Prognostic factors are defined as variables available at the time of treatment start that can estimate the chance of recovery or survival of a disease. They can reflect tumor biology, stage of disease, or personal traits of the patient. Predictive factors are factors that prior to or during therapy can predict the likelihood of response to a particular treatment. Studies of prognostic factors can help us to identify patients with a better prognosis, where treatment might be de-escalated; or a worse prognosis, where we might need to intensify treatment or search for other options. Research on prognostic and predictive factors can also give us valuable insights in tumor biology.

Epithelial ovarian cancer

Stage at diagnosis is the most important prognostic factor in epithelial ovarian cancer. Patients with FIGO stage I have an excellent five-year OS rate of 90%, whereas patients diagnosed with FIGO stage IV only have an OS of 20% at five years (14).

Besides FIGO stage, age at diagnosis has a large impact on prognosis, due to multiple factors. Elderly patients are more likely to be diagnosed with more advanced stage, lower differentiated tumors, and they are less likely to be fit enough to undergo radical surgery and intense chemotherapy (due to both age and comorbidity) (96). Radical primary surgery improves prognosis, with a 5.5% increased median survival with every 10% increase of tumor reduction (97). BRCA1 and BRCA2-mutations are associated with improved survival and better response to platinum-based chemotherapy (98) as well as sensitivity to PARP-inhibitors (drugs inhibiting the enzyme poly (ADP-ribose) polymerase) (99). Different histopathological factors have also been proven to be prognostic, with a better outcome in patients whose tumors are positive for estrogen and progesterone (100, 101) as well as for tumors rich in lymphocytes (102, 103). There are no established lifestyle-related prognostic factors in ovarian cancer.

Since reproductive factors, in particularly parity, reduce the risk of developing epithelial ovarian cancer (64), this leads to the question of whether these factors also influence the prognosis. Previous studies have not been consistent, but most studies found a trend towards better prognosis in parous women (104-110). Moreover, only one study stratified results by ovarian cancer subtype (104). Results from studies on the prognostic effect of parity in epithelial ovarian cancer are summarized in Figure 3 and Table 5 (by parts adapted from Poole et al (111)). Due to the possible association in the majority of studies, indicated by the low point estimates, my hypothesis prior to conducting my third study was that childbirth would potentially be advantageous from a prospective perspective.

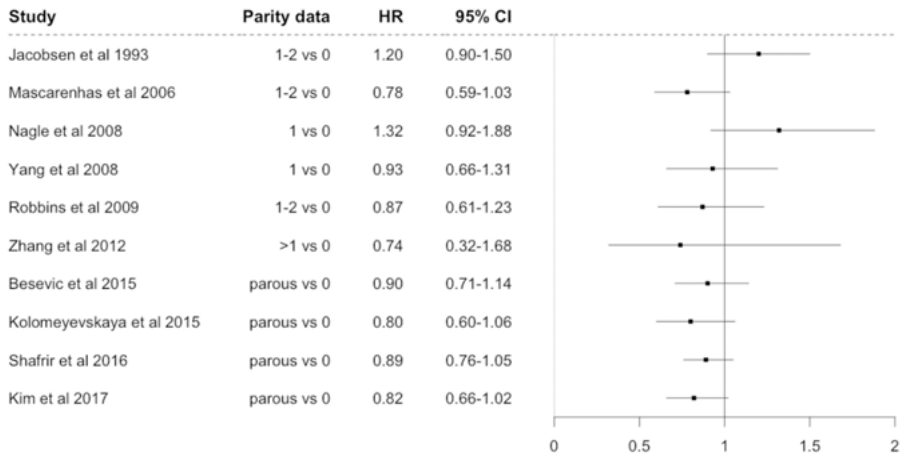

Figure 3. Parity and prognosis in previous studies on epithelial ovarian cancer.

Table 5. Prior studies on parity and prognosis of epithelial ovarian cancer show inconsistent results, but the majority indicate a better prognosis in parous women than in nulliparous women (by parts adapted from Poole et al 2016(111)).

Study (year)	Number	Result No. of births, HR (95% CI)	Covariates adjusted for
Jacobsen et al. (1993) (112)	644 cases, 419 deaths	1–2 vs 0, HR: 1.2 (0.9–1.5) 3–4 vs 0, HR: 0.9 (0.7–1.3) 5+ vs 0, HR: 0.9 (0.6–1.5)	Age, stage, decade of diagnosis
Mascarenhas et al. (2006) (106)	649 invasive cases, 344 deaths	1–2 vs 0, HR: 0.78 (0.59–1.03) 3–4 vs 0, HR: 1.02 (0.74–1.41)	Age
Nagle et al. (2008) (113)	676 cases, 419 deaths	1 vs 0, HR: 1.32 (0.92–1.88) 2 vs 0, HR: 1.01 (0.74–1.35) 3 + vs 0, HR: 0.91 (0.67–1.22)	Stage, age group, grade, res. disease, smoking status
Yang et al. (2008) (109)	635 cases, 396 deaths	1 vs 0, HR: 0.93 (0.66–1.31) 2 vs 0, HR: 0.81 (0.61–1.09) ≥ 3 vs 0, HR: 0.91 (0.67–1.24)	Age, stage, grade
Robbins et al. (2009) (107)	410 cases, 212 deaths	1–2 vs 0, HR: 0.87 (0.61–1.23) ≥ 3 vs 0, HR: 0.92 (0.64–1.33)	Age, stage
Zhang et al. (2012) (110)	195 cases, 79 deaths	≥ 2 vs 0, HR: 0.74 (0.32–1.68)	Age, BMI, menopausal status, stage, grade, ascites, chemotherapy
Besevic et al. (2015) (104)	1025 cases, 511 deaths	Parous vs nullip., HR: 0.90 (0.71–1.14) Serous: HR: 0.96 (0.69-1.33)	Age, year, BMI, stage, smoking status
Kolomeyevskaya et al. (2015) (105)	387 cases	Parous vs nullip., HR: 0.80 (0.60-1.06)	Stage, age at diagnosis, histology
Shafrir et al. (2016) (108)	1649 cases, 911 deaths	Parous vs nullip., HR: 0.89 (0.76-1.05) Only adjusted for age, year, menopausal status, smoking, BMI: HR: 1.19 (1.02-1.40)	Age, year, study center, menopause status, smoking, OC use, BMI, stage, grade, histology, debulking status
Kim et al. (2017) (114)	1394 cases, 638 deaths	Parous vs. nullip., HR: 0.82 (0.66-1.02) Sub-cohort, adj for res. disease: HR: 0.71 (0.54-0.93)	Age, histology, stage (+res. disease in sub-cohort)

Abbreviations: adj: adjusted; BMI: body mass index; CI: confidence interval; HR: hazard ratio; no.: number; nullip.: nulliparous; OC use: oral contraceptive use; res. disease: residual disease; vs: versus

Non-epithelial ovarian cancer

The five-year relative survival in non-epithelial ovarian cancer exceeds 90% in GCTs (14, 115) and is almost as good in SCSTs (50). Advanced disease stage is the most important negative prognostic factor. Very few prognostic factors besides age and stage exist, although treatment and disease presentation vary within the different subtypes (52). Tumor rupture during surgery seem to be prognostic in SCSTs (48), and for GCTs, incomplete surgical resection and yolk sac tumor histology seem to have a negative impact on prognosis (51). To our knowledge, no one has studied whether the prognosis in non-epithelial ovarian cancer is affected by parity.

Hypothesis hormones and risk of epithelial ovarian cancer

I have summarized the existing hypothesis for specifically epithelial ovarian cancer risk in a recent review on risk of different cancer types after pregnancies. This is illustrated below (Troisi,… **Sköld,**… et al 2018) (116).

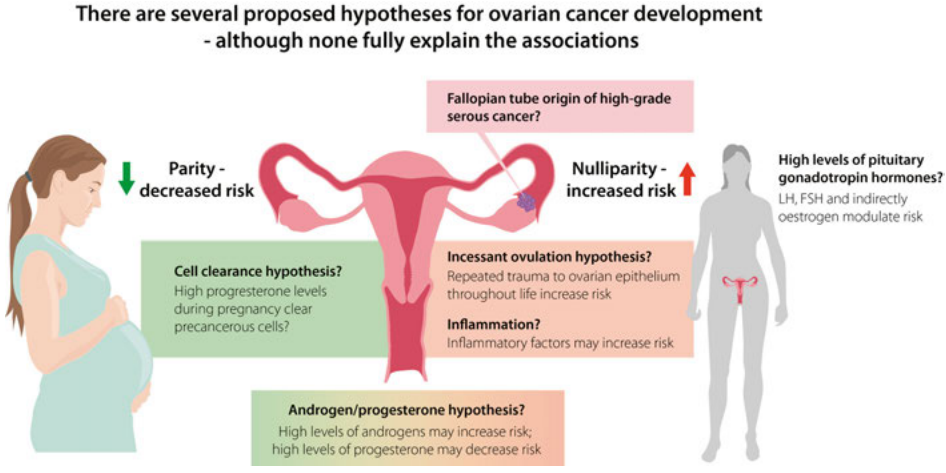

Figure 4. Hypothesis of ovarian cancer development. From Troisi et al (116), with permission from Wiley.

Although it has been known for a long time that pregnancies and oral contraceptives provide a risk reduction against epithelial ovarian cancer, the underlying mechanism has still not been revealed. Several hypotheses have been postulated (117); I specifically address the cell clearance hypothesis in this thesis.

Incessant ovulation hypothesis

The most cited is the incessant ovulation hypothesis. It states that the repeated ovulatory trauma and repair of the ovarian epithelium increases the risk of malignant transformation. Ovulation also exposes the ovarian and fallopian tube epithelium to follicular fluid with high estrogen concentrations, which might be of importance (see section Inflammation below). Thus, factors that

inhibit ovulations such as oral contraceptives and pregnancies decrease the risk of cancer development (118). However, the hypothesis is unable to explain why nine months of anovulation provided by pregnancy has a stronger protective effect than the same period of anovulation caused by other factors. Even with the addition of one year of anovulation by lactation, the protection is still stronger than for example one year of anovulation caused by oral contraceptives. Further, several years of later menarche or earlier menopause seem to have a limited impact on ovarian cancer risk, and although polycystic ovarian syndrome (PCOS) causes anovulatory cycles, it does not decrease the ovarian cancer risk (119).

Inflammation

Inflammatory conditions have been proposed to increase the risk of ovarian cancer. Ovulation induces a repeated inflammatory reaction both on the ovarian surface and in the fallopian tube, by exposure to the follicular fluid rich in steroids, cytokines, and free radicals. The inflammation can be cell damaging and mutagenetic (120). Further, it has been suggested that the use of non-steroid anti-inflammatory drugs (NSAIDs) reduces the risk of ovarian cancer (121). Endometriosis, which causes chronic inflammation in the pelvis, is associated with increased risk of endometrioid and clear cell ovarian cancer, but not with the other subtypes (122).

High levels of gonadotropin

An alternative explanation behind the protective effect provided by pregnancies and oral contraceptives is through the reduction of pituitary gonadotropins. Lower levels of gonadotropins are thought to increase the malignant transformation of the ovarian epithelium either directly through luteinizing hormone and follicle stimulating hormone or through estrogen stimulation (123). This is in line with the increase in incidence rate in early postmenopausal years when levels of gonadotropins increase.

Androgen/progesterone

The androgen/progesterone hypothesis suggests that increased levels of androgens stimulate the ovarian epithelium, while high levels of progesterone decrease ovarian cancer risk by undefined mechanisms (124). It has been suggested that androgens promote ovarian cancer progression by inhibiting transforming growth factor beta 1 (TGFβ1, described more in detail later in the thesis) (125), and the cell clearance (described below) could be the mechanism whereby progesterone decrease the risk of ovarian cancer.

Cell clearance

A less cited theory is the cell clearance hypothesis, suggesting that high levels of progesterone (or possibly other hormones) during pregnancy induces clearance of precancerous cells from the epithelium of the ovary or fallopian tubes via apoptosis (80). This will result in a reduced risk of carcinogenesis during subsequent years after pregnancies, and could also explain the protective role of oral contraceptives. Pregnancy leads to a period of anovulation, reduces gonadotropin secretion and increases endogenous estrogen and progesterone levels. Furthermore, pregnancy temporarily interrupts the retrograde transportation of exogenous substances or menstrual blood through the fallopian tubes. Thus, this is consistent with all above-mentioned hypothesis. I will discuss the cell clearance hypothesis more in detail in my studies.

Parity and ovarian cancer biology

A systematic approach to understanding the complex biology defining a cancer cell has been described by Hanahan and Weinberg, who introduced the concept of six hallmarks of cancer in 2000 (126). The hallmarks describe essential biological capabilities a cancer cell has to attain during the multistep malignancy process: i.e. sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. The model was updated 2011 with two more hallmarks: deregulating cellular energetics and avoiding immune destruction, and two characteristics enabling all the hallmarks: genomic instability and mutation, and tumor-promoting inflammation (127).

As previously described, parous women have a long-lasting reduced risk of developing epithelial ovarian cancer. The hallmarks of cancer might provide insight into the underlying mechanism behind the parity-associated protection against ovarian cancer. Preclinical studies indicate that parity might affect tumor-promoting inflammation. In a mouse model of ovarian cancer, multiparous mice had lower serum levels of cytokines and better survival compared with nulliparous mice, suggesting parous mice have an improved immune response to ovarian cancer (128). Another study provided further evidence of a favorable immune profile of parous mice, and reduced tumor implantation in the omentum (129).

In breast cancer, pregnancies cause the breast epithelium to differentiate, which reduces the risk of breast cancer (130, 131). In ovarian cancer, there are few studies exploring whether childbirths effect tumor characteristics. An American study from 2009 (132) found no difference in ovarian tumor PR expression by parity status; nor in an updated version including additional cases and controls (133). However, increased number of children was associated with a lower risk of the combination of negative estrogen receptor-alpha/negative PR expression (133).

Every hallmark of cancer is a possible focus for targeted cancer therapies and is central in the concept of precision cancer medicine (Figure 5). In epithelial ovarian cancer, targeting genomic instability with PARP-inhibitors and angiogenesis with VEGF-inhibitors are the most prominent examples in clinic (134). Low-grade serous ovarian cancer has a high frequency of activating KRAS/BRAF mutations, possible to target with BRAF/MEK-inhibitors (targeting the hallmark “sustaining proliferative signaling”) (135, 136). Moreover, a subset of endometrioid and clear cell tumors is associated with micro

satellite instability and thereby a candidate for treatment with immune checkpoint inhibitors (137, 138). The still dismal prognosis in ovarian cancer calls for the need to continue exploring ways of targeting the malignant processes.

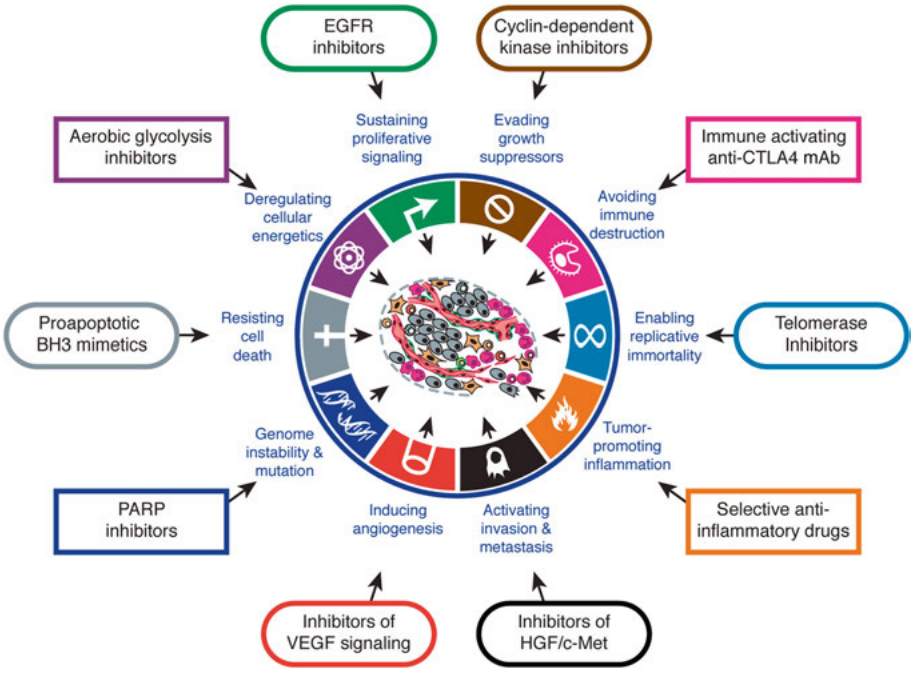

Figure 5. Hallmarks of cancer with therapeutic targets. From Hanahan and Weinberg (127), with permission from Elsevier.

By investigating proteins and hormones that increase in late pregnancy and how they influence different hallmarks of cancer (e.g., tumor-promoting inflammation, proliferative signaling, angiogenesis and growth suppressors), we might gain new insight into ovarian tumor biology and possibly find new targets for treatments. One step towards this characterization is to explore whether expression of certain proteins and hormones in the ovarian tumor differs between parous and nulliparous women.

Studied proteins

According to the cell clearance hypothesis (described previously), high levels of progesterone or other pregnancy hormones could possibly induce apoptosis in precancerous cells in the epithelium of the ovary or fallopian tubes. Some proteins and hormones of extra interest in this respect are described in this section. In addition to this, the role of estrogens is briefly discussed.

Progesterone

Progesterone is often called the "hormone of pregnancy", due to its importance in gestational maintenance. During the first weeks of pregnancy, increasing levels of human chorionic gonadotropin stimulate progesterone secretion from the corpus luteum. From around the 8th week of pregnancy, the placenta develops and takes over the progesterone production, with continuously increasing concentrations throughout the pregnancy (139), Figure 6. The serum progesterone concentration increases by 8% each week in the second to third trimester (140). Plasma concentration varies between women, with mean concentration around 50 ng/ml at 22 weeks to 150 ng/ml (100-300 ng/ml) at term (141). In non-pregnant women, progesterone is produced by the corpus luteum and mean serum concentration varies during the menstrual cycle between <1 and 20 ng/ml (142).

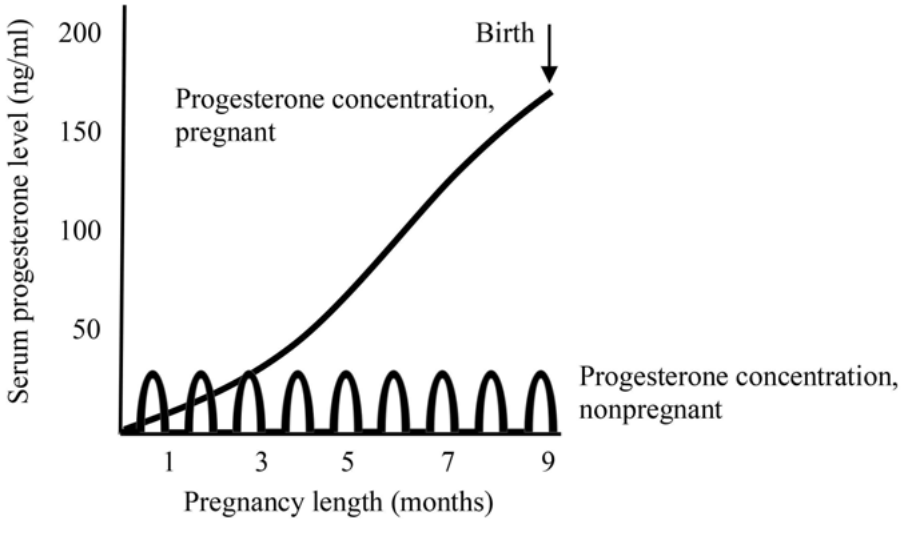

Figure 6. Serum progesterone concentrations during pregnancy.

Progesterone is the hormone most likely to eliminate premalignant cells during pregnancy, as proposed by the cell clearance hypothesis. As shown above, progesterone level increases substantially during pregnancy, and consistent preclinical studies have found a convincing apoptotic effect of progesterone and synthetic progestin. Progesterone has been shown to induce apoptosis, or inhibit growth, in ovarian cancer cells of both humans (143-147) and sheep (148), as well as in normal ovarian epithelial cells (149). Synthetic progestin has also been shown to induce apoptosis in ovarian cancer cell lines (150), as well as in epithelial ovarian cells of macaques (151, 152) and chicken (153) exposed to progestin. Moreover, the use of oral contraceptives with high-

progestin formulations seems to provide stronger protection against ovarian cancer compared with low-dose formulations (154).

Progesterone binds to the nuclear progesterone receptor (PR), which has two isoforms: A and B, only differing in 164 extra amino acids in PR B. In clinical practice, expression of PR A and B are not measured individually (155). High expression of PR in tumor tissue is associated with lower disease stage and improved ovarian cancer survival (100).

Progesterone receptor membrane component 1 (PGRMC1)

PGRMC1 is an anti-apoptotic protein involved in cancer development in a number of malignancies, including ovarian cancer (156-160). Its expression increases with more advanced ovarian cancer (161), and it has been proposed that PGRMC1 mediates progestins' carcinogenic impact in breast cancer (162). Progesterone can stimulate PGRMC1 expression in the ovary (163), and the expression of PGRMC1 in the corpus luteum of rats increases during pregnancy (164).

Relaxin-2

Relaxin, predominantly relaxin-2 in humans, is mainly produced by the corpus luteum. Serum levels rise during pregnancy, when it is also produced by the placenta and decidua, resulting in cervical and ligamental softening, development of mammary glands, vasodilatation etc. (165). It inhibits endometrial PR (166), and by upregulation of vascular endothelial growth factor (VEGF), relaxin-2 stimulates angiogenesis during both pregnancy and carcinogenesis (167-169). Higher concentration of serum relaxin-2 has been associated with adverse survival and tumor progression in several malignancies (170-172), including ovarian cancer (173).

Transforming growth factor beta 1 (TGFβ1)

TGFβ1 is a multipotent cytokine involved in reproductive processes and carcinogenesis. It plays an important role in the implantation process in early pregnancy, and in later pregnancy TGFβ1 inhibits placental hormonal production, including progesterone (174).

Interestingly, TGFβ1 has reversed roles in early and late cancer development. In the premalignant phase, TGFβ1 has a growth inhibitory and apoptotic effect on epithelial cells by upregulating cyclin-dependent kinase (CDK) inhibitors. However, later in the cancer development, the malignant cells become resistant to growth inhibitory signals and start producing TGFβ1 themselves. In more advanced malignant disease, TGFβ1 has a tumor-promoting effect, inducing epithelial-to-mesenchymal transition and the metastatic process (175, 176). It has been suggested that androgens promote ovarian cancer

progression by inhibiting TGFβ1 (125), and there are several indications that TGFβ1 inhibits the expression of PR in hormone-responsive organs (177).

Estrogens

Estrogen is the primary sex hormone in women, with multiple functions including sexual and reproductive development. The three major endogenous estrogens in humans are estrone (E1), estradiol (E2) and estriol (E3), all binding to ER alpha/beta. The estrogens are of varying importance during a woman's life; estradiol is the most important form during the reproductive years, while levels of estrones are higher in menopausal women (178). All estrogens are primarily synthesized in the ovaries by aromatization of androgens. During pregnancy, the placenta is the main producer of the steadily rising levels of estrogens, produced by converting androgens from both maternal and fetal adrenal glands (179). Estradiol concentrations rise from 1 ng/ml in early pregnancy to 6-30 ng/ml at 40 weeks (180, 181). Contrary to progesterone, estrogens seemingly have anti-apoptotic and proliferative effects on ovarian cancer cells (182-185). Consequently, estrogens are not in focus in my thesis.

How the above-described proteins/hormones affect the tumor biology in patients that later develops ovarian cancer is not previously known.

Aims of the thesis

To better understand how pregnancies and pregnancy-related factors influence ovarian cancer, my aim is to study the impact pregnancy-related factors have on risk, prognosis and tumor biology in more detail. My first two studies focus on ovarian cancer risk, while study three and four aim to investigate how the prognosis and the ovarian cancer biology are affected by the woman's reproductive history. More specifically, the aims of the thesis are to:

I Understand the impact of pregnancy-related risk factors on risk of epithelial ovarian cancer and its different subtypes [Study I] and non-epithelial ovarian cancer [Study II].

II Study whether parity has an impact on prognosis in both epithelial and non-epithelial ovarian cancer and their subtypes [Study III].

III Examine whether the woman's parity status affects expression of progesterone receptor (PR), progesterone receptor membrane component 1 (PGRMC1), relaxin-2, and transforming growth factor beta 1 (TGFβ1) in high-grade serous ovarian cancer [Study IV].

Patients and methods

Studies I and II

Patients

In Papers I and II, two different cohorts of patients were investigated, however similar methods for data linkage were used. In both studies, we linked data from the medical birth registers (MBR) and the cancer registers in Denmark, Finland, Norway and Sweden.

The medical birth registers

The MBRs were founded in 1973 (Denmark), 1987 (Finland), 1967 (Norway), and 1973 (Sweden). They contain information from prenatal, obstetric, and neonatal medical records and are based on the mandatory reporting of all births (186-190). A standardized form is completed by a health care provider shortly after birth and data on practically all deliveries are included. Information include data on the mother, mode of delivery and infants birth weight and length.

The cancer registers

The cancer registers, founded in 1943 (Denmark), 1953 (Finland and Norway), and 1958 (Sweden), are based on the compulsory reporting of all newly diagnosed primary cancer cases and include date of diagnosis and tumor histology. Case reporting is done by clinicians, pathologists and cytologists and is essentially complete (191-194).

Record linkage between these registers was enabled by the personal identification number assigned to each citizen and permanent resident in the Nordic countries at birth or upon immigration.

We included all parous women registered in the MBRs at childbirth, who had a subsequent diagnosis of epithelial ovarian cancer (Study I) or non-epithelial ovarian cancer (Study II) recorded. Cases and controls were free from other cancers at time of inclusion. Information on every pregnancy for each woman was included in the linkage to the MBR; however, since many women had their first childbirths prior to the start of the MBR, data were most complete for the most recent pregnancy before the case's date of diagnosis.

Ovarian cancer was defined by ICD-10/ICD-O-3 code C56.9, and by ICD-7 code 175.0 in Denmark before 1978 and in Sweden before 1993. For each case, we sampled up to ten female controls that were alive and cancer-free at the time of the case's diagnosis and who were registered in an MBR with a prior pregnancy lasting longer than 22 weeks. Controls were matched by country and the case's year of birth.

Exposures

We examined the following exposures: number of births at the time of matching; age at first and last birth; time since first and last birth; preeclampsia and multiple pregnancy (in any pregnancy). Pregnancy length in completed weeks and birth length and weight of the offspring were ascertained from the cases' and controls' most recent pregnancy before the cases' date of diagnosis. Many of the cases' first pregnancies occurred before the MBRs started, thus, the most recent pregnancy provided the most complete data. Information on smoking habits during (any) pregnancy was available in Denmark 1991-2010, Finland 1987-2012, Norway 1998-2013, and Sweden 1982-2013.

Statistical analyses

We used conditional logistic regression (conditioned on birth year of the case and country) to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for pregnancy-related factors and ovarian cancer risk by histological subtype. In analyses of pregnancy length and birth length/weight of offspring, women who were diagnosed with ovarian cancer within six months after giving birth were excluded to minimize the possibility that associations were related to preterm delivery due to the cancer. We performed analysis adjusted for number of births. R version 3.3.2 was used for all analyses (195).

Study III

Patients

Study III was based on data linkage from three Swedish registers: the cancer register and the medical birth register (previously described), and the cause of death register. We included women born 1953 and later to guarantee that they were at least 20 years (and hence of childbearing age) when the nationwide MBR started in 1973; diagnosed at age ≥18 years with invasive ovarian cancer in Sweden from 1990 to 2018 (Figure 7). Since ovarian, fallopian tube and primary peritoneal cancer have common histology and origin and are usually considered as one entity, they were all included and referred to as ovarian cancer (196). Ovarian cancer was defined using ICD-7 code 175.0 or ICD-O-

3 code C56.9; fallopian tube cancer by ICD-7 code 175.1 or ICD-O-3 code C57.0; primary peritoneal cancer by ICD-7 code 158 or ICD-O-3 code C48.1 or C48.2. The subtypes of epithelial and non-epithelial ovarian cancer were defined by ICD-O-2 and ICD-O-3 codes.

The Swedish cause of death register

The Swedish cause of death register contains high quality data on virtually all deaths of people registered in Sweden since 1961 (with additional data in a historic register from 1952). Since 2012, all deaths occurring in Sweden, also among people not registered in Sweden, are included in the register (197).

Exposures

We analysed associations with the reproductive variables' parity, number of births (before ovarian cancer diagnosis), age at first and last birth (<25, 25-29 and ≥30 years), and time since first and last birth (<10, 10-19 and ≥20 years). We also analyzed associations with age at diagnosis and disease stage. Due to limited data, number of births, age at first and last birth and time since first and last birth were not analyzed in non-epithelial ovarian cancer cases.

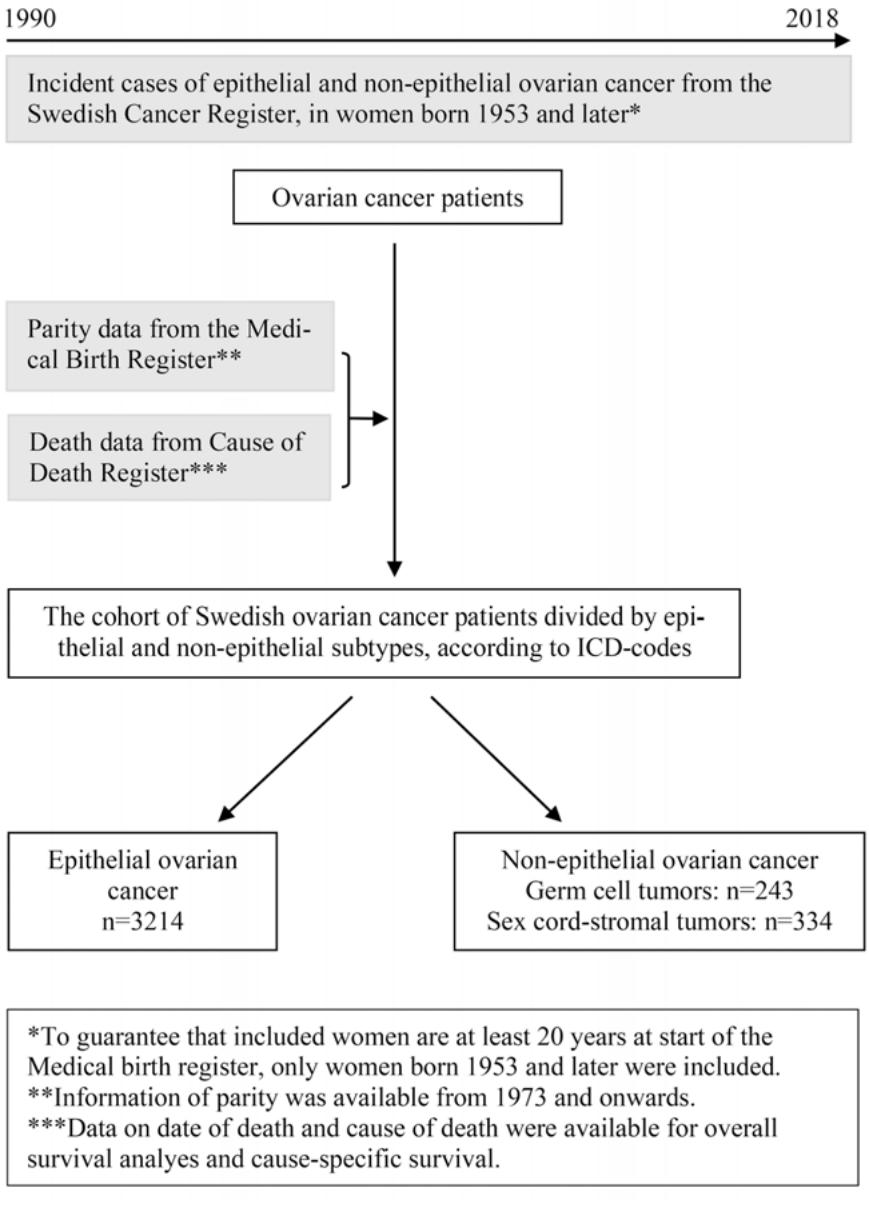

Figure 7. Flowchart of data linkages and inclusions and exclusions.

Statistical analyses

We used Cox-proportional hazard models to estimate hazard ratios (HRs) and 95% CIs for associations of pregnancy-related factors and survival, using both all-cause mortality and cause-specific mortality. Results were stratified on subtype of ovarian cancer (epithelial: serous, mucinous, clear cell, and endometrioid; non-epithelial: GCT and SCST). For cause-specific mortality, patients contributed with time from date of diagnosis until ovarian cancer death, and until death of any cause for all-cause mortality; or until end of follow up in February 2020. In cause-specific mortality analyses, women were censured at death from causes other than ovarian cancer. All results were adjusted for age at diagnosis, and in a subset of patients diagnosed 2003 and later, we additionally adjusted for disease stage. As a sensitivity test, we excluded cases diagnosed with ovarian cancer within six months after their last birth to minimize the possibility that survival of parous women was affected by earlier cancer detection due to the pregnancy. We also analysed associations excluding women with a cancer diagnosis prior to the ovarian cancer diagnosis, to ensure that a previous malignancy did not impact on the prognosis. We used the Kaplan-Meier method to illustrate cancer-specific survival in GCTs, stratified by age at diagnosis (<30 years and ≥30 years), and compared survival curves by log-rank tests. *P*-values were considered statistically significant if <0.05. All analyses were performed using RStudio version 1.2.1335 (198).

Study IV

Patients

Our patient cohort was identified in the Swedish cancer register, and all patients in Stockholm county aged 18 years or older who were diagnosed 2002-2006 with ovarian cancer, fallopian tube cancer or primary peritoneal carcinoma (as their first malignancy) were screened for eligibility. Inclusion criteria were high-grade serous histology, disease stage IIC-IV and available tumor tissue from biopsy or surgery performed before chemotherapy. Figure 8 presents inclusions and exclusions.

Assays

A tissue microarray (TMA) was constructed by tumor material (from ovarian tumor or implantation metastasis in omentum or peritoneum) from 136 chemo-naïve patients, as described earlier (199). In summary, representative tumor tissue was selected from formalin-fixed paraffin-embedded tumor tissue, stained with hematoxylin and eosin, and at least two cores of 1 mm diameter were taken from each patient. The TMA blocks were cut and stained for progesterone receptor A/B (PR), progesterone receptor membrane component 1 (PGRMC1), relaxin-2, and transforming growth factor beta 1 (TGFβ1). The staining was performed with an automated protocol using the DAKO Autostainer Link 48 platform.

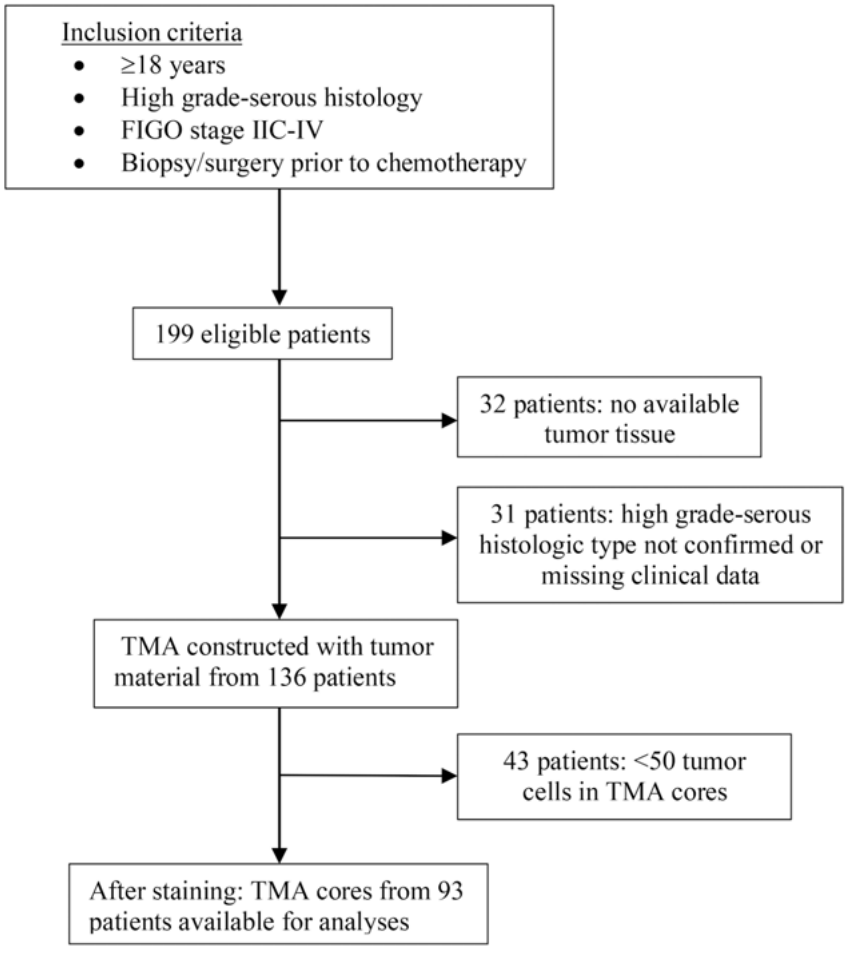

Figure 8. Flowchart of inclusions and exclusions of patients.

Scoring

Two independent observers (C.S. and A.K.), blinded to patient data, scored all cases, and a gynecological pathologist (A.T.) confirmed difficult cases.

The scoring was based on:

Percentage of positive cytoplasmic staining in tumor cells (PR, PGRMC1 and TGFβ1)

a. Negative (0): <1%
b. Weak (1): 1-24%
c. Moderate (2): 25-49%
d. Strong (3): ≥50%

2) Expression intensity (PGRMC1, relaxin and TGFβ1)
    a. Weak (1)
    b. Moderate (2)
    c. Strong (3)
3) Combined score of percentage and intensity (PGRMC1 and TGFβ1)
    By multiplying percentage of positive cells (grade 1-3) with intensity (grade 1-3), a score of 1-9 was obtained. The score was then merged to create a binary score (0-2 versus 3-9 points).

PR intensity was only based on percentage of positive cells as in clinical practice, and since relaxin-2 was expressed in virtually all tumor cells, only expression intensity was scored. If more than one tumor sample was available from a patient, we assessed the cores independently and used the maximum expression in our analyses. Representative examples of immunostaining evaluations are illustrated in Figure 9.

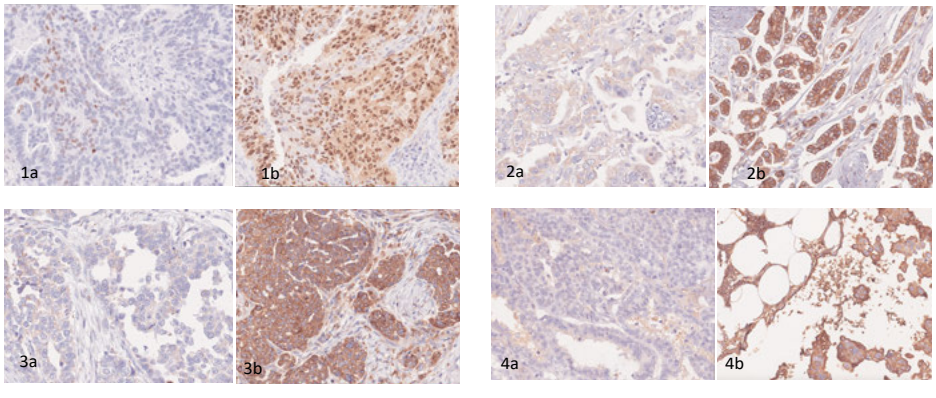

Figure 9. Representative examples of immunostaining results for tumors staining weak (1a) and strong (1b) for progesterone receptor; weak (2a) and strong (2b) intensity of progesterone receptor membrane component 1, weak (3a) and strong (3b) intensity of relaxin-2; and weak (4a) and strong (4b) intensity of transforming growth factor β1. Original magnification x200.

Statistical analysis

We used Chi-square test to assess differences in expression of PR, PGMRC1, relaxin-2 and TGFβ1 by the woman's parity status. In these analyses, negative/weak expression was compared with moderate/strong expression. We stratified expression of PR, PGMRC1, relaxin-2 and TGFβ1 by disease stage, and by year of birth (before 1935, 1935-1944, 1945 and later) by Fisher's exact test, to reflect on changes in use of oral contraceptives during different time periods.

Logistic regression models were constructed to estimate ORs with 95% CIs for association with positive expression of PR, PGMRC-1, relaxin-2, TGFβ1, respectively, by parity-status (parous versus nulliparous) or number of children (1-2 children and >2 children). The models were adjusted for age at diagnosis and disease stage. Internal correlation between expression of PR, PGMRC-1, relaxin-2 and TGFβ1 was estimated by the Spearman two-tailed test.

Patients were followed from diagnosis until ovarian cancer death (for cause-specific mortality); death of any cause (for all-cause mortality); or end of follow up (January 2020), and we censured patients at death from other causes in analyses of cause-specific mortality. We used the Kaplan-Meier method to visualize cancer-specific survival rates by expression of PR, PGMRC1, relaxin-2 and TGFβ1. Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% CI for associations between expression of PR, PGMRC1, relaxin-2, TGFβ1 and cancer-specific mortality, as well as all-cause mortality, adjusted for age at diagnosis and disease stage. Additionally, in a sensitivity analysis, we adjusted results for macroscopic residual disease after surgery (among patients who underwent surgery). *P*-values were considered statistically significant if <0.05. All analyses were performed using RStudio version 1.2.1335 (198).

Results

In summary, the main findings were:

I. Going through a full-term pregnancy was associated with decreased risk of epithelial ovarian cancer. Being multiparous, and being older at childbirth, were also associated with decreased risk [Study I].
II. Older age at last birth was associated with decreased risk of sex cord-stromal tumors, as was having a short time since last birth [Study II].
III. Parous women had a better prognosis in ovarian germ cell tumors, whereas no evidence of associations was found in patients with sex cord-stromal tumors or epithelial ovarian cancer [Study III].
IV. Increased number of children was associated with more pronounced progesterone receptor expression in tumor cells [Study IV].

Study I

We identified 10,957 cases of epithelial ovarian cancer among parous women, with a median age at ovarian cancer diagnosis/matching of 52 years. Analysis by histological subtype was possible for 7,971 cases.

Shorter pregnancy length in a woman's last pregnancy was associated with an increased risk of epithelial ovarian cancer (compared with a full-length pregnancy), and the shorter the pregnancy was, the stronger the association was; i.e., pregnancy length <30weeks versus 39-41 weeks: OR 1.33 (95% CI 1.06-1.67) (Figure 10). The results were unchanged when adjusted for age at first or last birth and smoking and did not vary by number of births.

Older age at first and last birth was associated with a decreased risk. Increased number of births was protective for all subtypes, with additional risk reduction for each subsequent birth. The risk reduction was most pronounced for clear-cell tumors. We found no associations with multiple pregnancies, preeclampsia or offspring size and epithelial ovarian cancer risk. In conclusion, in addition to high parity, full-term pregnancies and pregnancies at older age were associated with decreased risk of ovarian cancer.

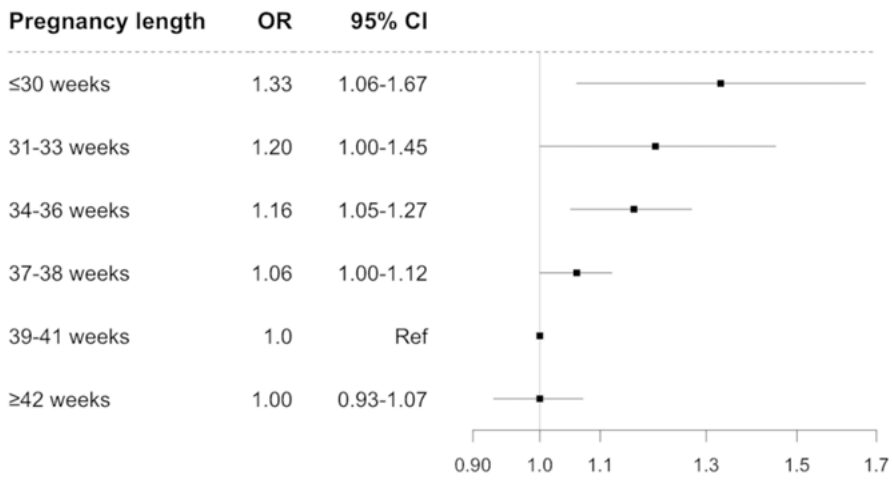

Figure 10. The risk of epithelial ovarian cancer associated with pregnancy length (data from last pregnancy).

Study II

The study included 345 cases of GCTs, with a median age of 37 years, and 420 cases of SCSTs, with a median age of 47 years at diagnosis/matching. Older age at last birth was associated with decreased risk of SCSTs (Figure 11), and a similar trend was seen with older age at first birth. SCST risk decreased gradually with increasing age at first or last birth. A recent childbirth (shorter time since first and last birth) was also associated with decreased risk. Increased number of births, multiple pregnancies, preeclampsia, pregnancy length, and offspring size, were not associated with risk of SCSTs. None of the investigated factors were associated with risk of GCTs.

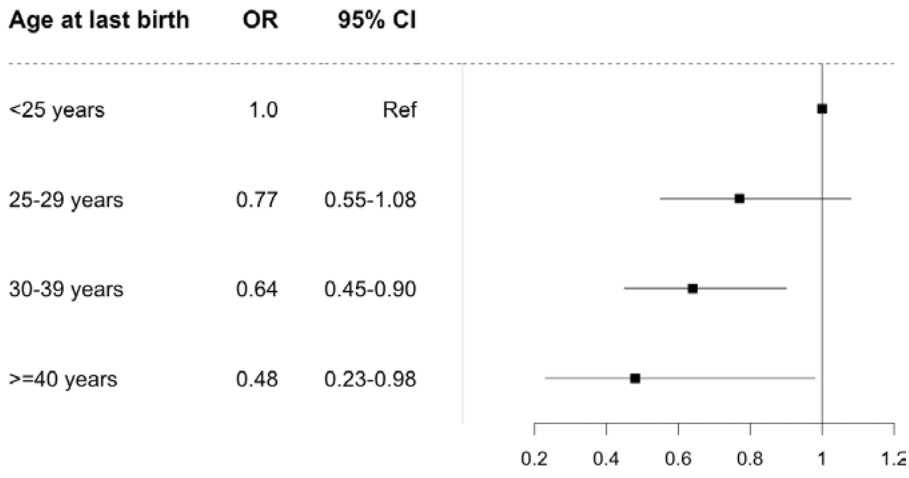

Figure 11. The risk of sex cord-stromal tumors was associated with age at last birth.

Study III

We evaluated the association between reproductive factors and cancer-specific mortality in 243 cases of GCTs, 334 of SCSTs, and 3214 epithelial ovarian cancer cases, stratified by cancer subtype. Parity was associated with 78% decreased risk of cancer-specific mortality in GCTs. No evidence of associations between reproductive history and prognosis in SCSTs or epithelial ovarian cancer was found.

When stratified on age at diagnosis, parity was only associated with reduced mortality in women diagnosed with GCTs at age 30 years or older. Most deaths in GCTs were seen in the teratoma subtype. Among women who were 30 years or older when they were diagnosed with teratomas, 6% of the parous women died of their disease, compared with 23% of the nulliparous women (*p*-value: 0.03).

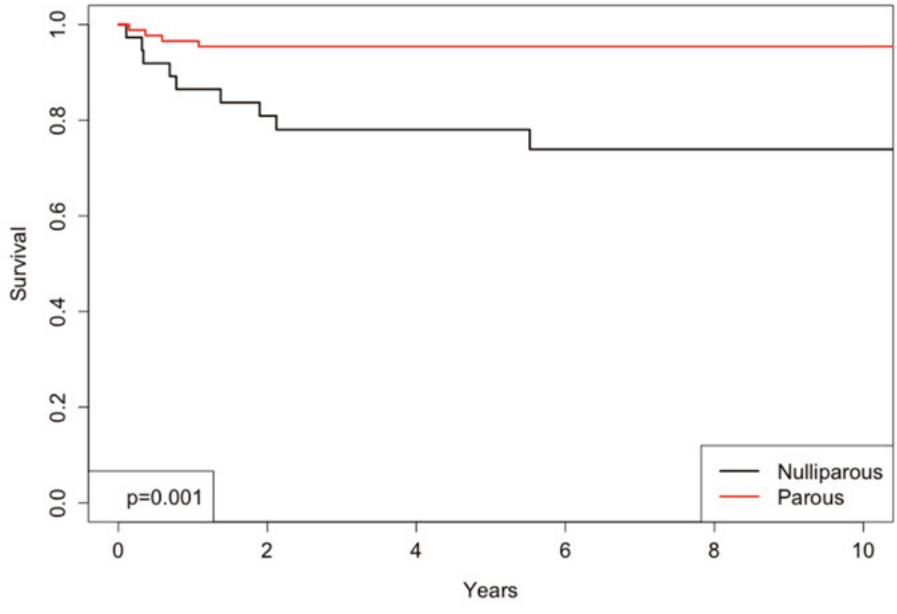

Figure 12. Kaplan-Meier curve of cancer-specific survival by parity status among women diagnosed with invasive ovarian germ cell tumors at age ≥30 years in Sweden 1990-2018 (n=124). *P*-value from log-rank test.

Study IV

Parous women had PR-positive tumors more often in comparison to nulliparous women. Increased number of children was associated with PR positive tumors; i.e., >2 children versus 0 children, adjusted for age at diagnosis and FIGO stage: OR 4.31 (95% CI 1.12-19.69). No difference was seen between parity status and expression of PGRMC1, relaxin-2 and TGFβ1. None of the studied hormones and proteins were independently associated with survival.

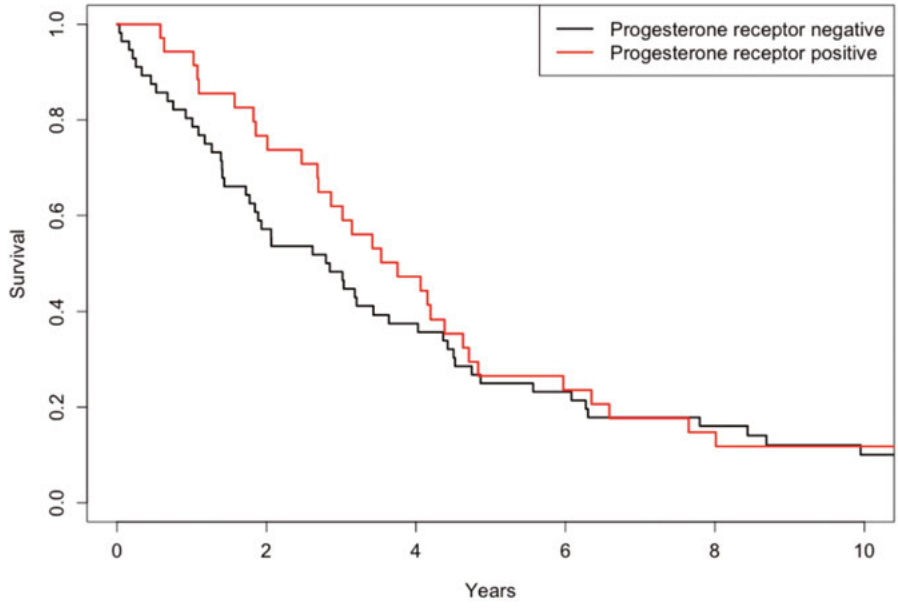

Figure 13. Kaplan Meier curve of cancer-specific survival for patients diagnosed with high-grade serous ovarian cancer 2002-2006 by expression of progesterone receptor A/B.

Discussion and conclusions

Studies I and II

We found that preterm birth was associated with an increased risk of epithelial ovarian cancer among parous women, whereas increased number of births and pregnancies at an older age were associated with decreased risk. Increasing age at last birth was also associated with lower risk of SCSTs, as was shorter time since last birth.

Our finding that full-term pregnancies provide the strongest risk-protection against epithelial ovarian cancer is supported by previous results in earlier, smaller studies (78, 79). Interestingly, full-length pregnancies seem to also be important in reducing the risk of breast cancer (200). The effect of age at birth, however, is the reverse in breast cancer, where a first childbirth at a younger age is more protective than a pregnancy at an older age (200). Our findings of a risk-reducing effect with increasing pregnancy length, as well as with older age at birth, favor the cell clearance hypothesis. Since hormone levels that mediate cell clearance, tentatively progesterone, increase during the last trimester of pregnancy, the association we found with increased risk with shorter pregnancy length is consistent with the cell clearance hypothesis. Moreover, since the risk of accumulating premalignant cells increases with both increasing time since pregnancy and older age at pregnancy, our finding that shorter time since last pregnancy, and pregnancies at an older age (a more recent cell clearance), are associated with lower risk of both epithelial ovarian cancer and SCSTs, are also in line with the cell clearance hypothesis. The incessant ovulation hypothesis would explain neither the increased risk associated with a few weeks' shorter duration of pregnancy, nor the lower risk seen in women with increasing age at pregnancy.

A strength in both studies I and II was the large sample sizes, with a sufficient number of patients to investigate uncommon pregnancy-related exposures and disaggregate the results by ovarian cancer subtype. A major weakness in both studies was lack of information on possible confounders, especially use of oral contraceptives. However, in previous studies on epithelial ovarian cancer, adjustment for oral contraceptive use did not alter associations with parity, number of births, or age at birth. Moreover, women born before 1940 are less likely to have used oral contraceptives, and since our results did not vary by birth year of the women, they are less likely to be altered by oral contraceptive use. In non-epithelial ovarian cancer, there are no established

risk factors, although associations with oral contraceptives have been suggested.

Both studies were restricted to parous women, since pregnancy-related factors were the exposures of interest, and hence, we could not study associations of being parous compared with nulliparity. Since parity is an established protective factor against epithelial ovarian cancer, this is not a major concern in this malignancy. In non-epithelial ovarian cancer, however, it would have been of greater importance to have nulliparous controls and thereby be able to study the effect of parity as a risk factor.

We found that going through a full-term pregnancy was associated with a decreased risk of epithelial ovarian cancer. In addition, an increased number of births and pregnancies at older age was associated with decreased risk. Older age at last birth was also associated with lower risk of SCSTs, as was shorter time since last birth.

Study III

Our large cohort enabled us to study associations stratified by subtypes of both epithelial and non-epithelial ovarian cancer, which has never been done previously. Even though reproductive factors are seemingly of limited importance for risk of developing non-epithelial ovarian cancer (Study II), we found that parous women had a 78% decreased risk of cancer-specific mortality in GCTs. Among women aged ≥30 at diagnosis in our study, only 4% of parous women died during follow-up, compared with 23% of nulliparous women. This indicates that parous women might develop less aggressive tumors, possibly by differentiation of pre-carcinous cells during pregnancy. The better prognosis in parous women is not likely to be caused by social factors, e.g., a stronger social network among women with children, since women in our study were young and hence, dependence on family is less likely to effect mortality. Moreover, it is difficult to explain why the effect would be pronounced only in GCTs and not in the other ovarian cancer subtypes.

Despite the comparably large study size, statistical power was limited when calculating associations with especially GCTs and SCSTs. Among limitations was also lack of information on possible confounders, such as infertility and body mass index; however, these factors have not been associated with prognosis in GCTs. Information on disease stage was limited to the time period 2003-2018. We also lacked information on comorbidities; but since women with GCTs were young, it is unlikely that comorbidities had an impact on survival.

Figure 14. Previous results and the associations found in this study (in part adapted from Poole et al (111)).

Since we only included women born 1953 and later in the study, mean age at diagnosis among women with epithelial ovarian cancer only 48 years. This makes our results representative mainly for women who are relatively young at diagnosis. However, it is not likely that the prognostic importance of parity would be more notable with increasing time since childbirth (as being older at diagnosis would lead to). In GCTs, the subtype where parity was associated with better prognosis, the mean age was only 32 years, but these rare tumors are most common in teenagers and young women.

Study IV

Our hypothesis was that high levels of progesterone (or possibly other pregnancy hormones) would impact on tumor precursor cells, which could result in different tumor receptor expression in the developed tumor even many years after childbirth. We found that tumors from parous women expressed PR more often than tumors from nulliparous women, in line with our hypothesis. A possible explanation could be that the epithelium in the distal fallopian tube, the believed origin of HGSOC, matures during pregnancy, and that tumor cells thereby are more likely to express PR. Our findings do not strengthen the cell clearance hypothesis, neither do they contradict it. If high progesterone levels during pregnancy were to clear premalignant cells, a tumor evolving years later could originate from cells whose malignant transformation began after the pregnancy occurred (and hence did not undergo cell clearance). A possible idea to explore this topic further is discussed in Future perspective.

Among the strengths of our study is the well-defined, Swedish Cancer register-based cohort and the detailed clinical data obtained from patient charts, excluding the risk of recall bias. The cohort is homogenous, encompasses only HGSOC patients, specifically reviewed and re-assessed. The aim of creating a highly controlled and homogeneous study cohort limited the number of participants, and restricted our possibilities to find associations and to stratify results into subgroups. Another bias might be our binarization criteria of the pathology scores, which were partly arbitrary.

We lacked information on oral contraceptive use and hormonal replacement treatment. Oral contraceptives were introduced in Sweden during the 1960s, increased during the following decades and are used mostly by younger women. This implies that women born before 1935 are less likely to have used oral contraceptives. Since the proportion of PR positive tumors was not different among women born before 1935 than among women born 1935-1944 or after 1945, it is less likely that oral contraceptive use has a major impact on PR expression in our study.

Conclusion and clinical relevance

I. Not only increased number of births, but also other pregnancy-related factors such as longer pregnancy-length (in epithelial) and older age at childbirth (in both epithelial and sex cord-stromal tumors) had risk-reducing effects on ovarian cancer.
II. Parity had an impact on ovarian cancer prognosis only in women diagnosed with germ cell tumors, where parous women had better cancer-specific survival.
III. The woman's parity status had an impact on tumor expression of progesterone receptor, with more pronounced expression with increased number of childbirths, but not on expression of progesterone receptor membrane component 1, relaxin-2, or transforming growth factor beta 1.

In conclusion, we found that full-length pregnancies and giving birth at an older age provided the strongest protection against ovarian cancer and its subtypes (Studies I and II), in line with the cell clearance hypothesis. The prognostic effect of parity seems to be limited, except in GCTs where parous women had better cause-specific survival (Study III). Pregnancies seem to have an effect on tumor histology, since number of children impacted on PR expression in HGSOC (Study IV). Taken together, my results suggest that factors in late pregnancy provide long-lasting effects on the malignant development in the fallopian tube/ovary. An apoptotic effect on pre-malignant cells could be provided by high pregnancy-levels of progesterone, a hypothesis needing further exploration. If we could mimic the process whereby pregnancy reduces ovarian cancer, e.g., by treating women at high risk of ovarian cancer with pregnancy-equivalent doses of progesterone/progestin, clearance of premalignant cells could be achieved and thereby reduce ovarian cancer risk. A major concern is however that women with high risk of ovarian cancer are most often also at risk of breast cancer, where progesterone is believed to increase risk. A possible approach could be to develop selective PR modulators that would only bind to gynecological PR and not affect mammary tissue.

Future perspective

The increased risk of ovarian cancer in patients with *BRCA1* or *BRCA2*-mutations and Lynch syndrome have not been specifically addressed in my register-based investigations (201, 202), due to non-registered data. Genetic/environmental interactions may be of importance, and it would be of interest to see if also environmental exposures (such as pregnancies) impact on genetic abnormalities. It would similarly be interesting to further study whether the woman's obstetric history has an influence on the tumor biology and genetic alterations in ovarian cancer, by analyzing associations between pregnancies and protein expression in tumor tissue and specific genetic alterations.

A possible explanation behind higher PR expression in tumors from parous women could be that the epithelium in the distal fallopian tube, the main origin of HGSOC, differentiates during pregnancy, and that tumor cells thereby are more likely to express PR. This would be in line with results in breast cancer, where pregnancies will cause differentiation of glandular tissue and thereby reduce the breast cancer risk (130). In hormone-dependent luminal breast cancer, parity has however been associated with reduced risk of PR positive tumors (203); but diverse effects might be seen in different cancer types. By evaluating PR expression in fallopian tube cells from ovariectomies of risk subjects (e.g., *BRCA*-mutated patients) and comparing them with healthy controls, we could possibly gain insight into this question.

Little is known about risk factors in non-epithelial ovarian tumors, highlighting the need of future, well-designed studies. It would be of value to further explore the importance of parity on risk of GCTs and SCSTs in an epidemiologic study including nulliparous controls. If parity leads to differentiation of premalignant cells, as hypothesized in study II, the effect would be most obvious when comparing nulliparous with parous women (and not number of children among parous women). Moreover, since deaths in teratomas seem to explain the difference in cancer-specific mortality between parous and nulliparous women with GCTs, it would be interesting to study whether gene expression or hormonal receptor expression differs by parity in tumor samples.

Sammanfattning på svenska (Summary in Swedish)

Äggstockscancer är den dödligaste gynekologiska cancersjukdomen, vilket gör forskning om denna tumörform extra betydelsefull. De bakomliggande orsakerna är inte fullt klarlagda, delvis på grund av att äggstockscancer inte är en distinkt sjukdom utan snarare utgörs av flera olika undergrupper. Den vanligaste formen har sitt ursprung i äggstockens yttre cellager, kallat epitel (”epitelial äggstockscancer”, 90%), medan 10% uppstår i könssträngs-stromaceller eller könsceller inuti äggstocken (”icke-epitelial äggstockscancer”). Epitelial äggstockscancer är vidare uppdelad i olika undertyper som har olika bakgrund och sjukdomsförlopp. Kvinnor som fött barn har mindre risk att utveckla epitelial äggstockscancer, och risken minskar ytterligare med varje barnafödsel. Huruvida även andra graviditetsrelaterade faktorer, som havandeskapsförgiftning, graviditetens längd, moderns ålder vid barnafödande och barnets storlek, påverkar risken för äggstockscancer har inte varit känt. Vidare har det inte varit klarlagt om graviditet påverkar risken för icke-epitelial äggstockscancer. Man har heller inte klargjort mekanismen bakom barnafödandets skydd mot äggstockscancer, och graviditeters betydelse för överlevnaden i äggstockscancer har hittills varit oklar.

I mina första två arbeten undersökte jag sambandet mellan faktorer kopplade till graviditeten och risken för att drabbas av epitelial äggstockscancer och dess undertyper (artikel I) och icke-epitelial äggstockscancer och dess undertyper (artikel II), genom länkning av data från nordiska födelse- och cancerregister. I artikel I fann jag att för tidig födsel var associerat med en ökad risk för epitelial äggstockscancer bland kvinnor som fött barn, medan ökat antal barn och graviditet vid högre ålder var associerat med lägre risk. I artikel II fann jag att högre ålder vid sista barnafödseln, liksom kortare tid sedan senaste födseln, var kopplat till en lägre risk för undertypen könssträngs-stromacellstumörer.

I artikel III undersökte jag barnafödandets betydelse för överlevnaden i både epitelial och icke-epitelial äggstockscancer och dess undertyper genom länkning av data från Medicinska födelseregistret, Cancerregistret och Dödsorsaksregistret i Sverige. Barnafödande var associerat med en minskad risk för cancerspecifik dödlighet i könscellstumörer, en undertyp av icke-epitelial äggstockscancer. Jag fann inget samband mellan barnafödande och

cancerspecifik dödlighet bland patienter med könssträngs-stromacellstumörer eller epitelial äggstockscancer.

I artikel IV undersökte jag om uttrycket av hormoner och proteiner involverade i graviditet och tumörutveckling påverkades av kvinnans tidigare barnafödande, i patienter med undertypen höggradig serös äggstockscancer. Kvinnor som fött barn hade oftare tumörer som uttryckte progesteronreceptorer än kvinnor som inte fött barn, och ökat antal barn var kopplat till progesteronreceptor-uttryck.

Sammanfattningsvis har kvinnans barnafödande inverkan inte bara på hennes risk att utveckla äggstockscancer, utan också en långvarig påverkan på tumörbiologin. Målet med min forskning är att öka kunskapen kring graviditetens betydelse vid äggstockscancer och därmed bidra till utveckling av nya strategier för att både förebygga och behandla denna dödliga sjukdom.

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